



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FEB 17 2000

Food and Drug Administration  
Rockville MD 20857

Our Reference Number: 99-0279 and 99-0724

Jack D. Love, Ph.D.  
Lederle Laboratories Division  
American Cyanamid Company  
211 Bailey Road  
W. Henrietta, NY 14586

Dear Dr. Love:

Your Biologics License Application for Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) \_\_\_\_\_ "Prennar," for the immunization of infants at 2, 4, 6 and 12-15 months of age to prevent invasive pneumococcal disease, is approved this date. Lederle Laboratories, Division of American Cyanamid Company, is hereby authorized to introduce or deliver into interstate commerce, Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) produced at your Sanford, North Carolina and Pearl River, New York locations under U.S. License No. 17.

The dating period for this product shall be 24 months from the date of manufacture when stored continuously at 2-8°C. The final formulated bulk may be stored for up to \_\_\_\_\_ and no more than \_\_\_\_\_ in final container, when maintained at 2-8°C. The date of manufacture shall be defined as the date of initiation of the last valid potency test on the final formulated bulk. Any extension of the dating period will require the submission of supporting data as a supplement to your biologics license application for review and approval. Alternatively, you may submit a stability protocol to be used in extension of dating as a supplement to your license application.

You are requested to submit to the Center for Biologics Evaluation and Research (CBER) samples of each future formulated bulk together with protocols showing the results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, CBER.

We acknowledge your commitments dated November 2, 1999, December 10, 1999, and February 14, 2000, for the following manufacturing issue, as well as Phase 4 clinical studies and data:

1. You have agreed to establish alert and action limits for the amount of residual \_\_\_\_\_ in the final polysaccharides. The data justifying alert and action limits will be submitted to CBER by the 1<sup>st</sup> Quarter of 2001.

2. You have agreed to obtain additional safety data for previously unvaccinated children who receive Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) according to recommendations for "catch-up" immunization. A study(s) will evaluate reactogenicity of vaccination for the age groups 7 months to less than 2 years, 2 years to less than 5 years, and 5 years to — years. This study will be initiated in April 2000.
3. You have agreed to initiate a Phase 4 study to evaluate less common adverse events in — children who will receive — doses of Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) concomitantly with routinely recommended childhood vaccines, e.g., DTaP, *Haemophilus influenzae* type b conjugate vaccine, IPV and hepatitis B vaccine. This study will be initiated in April 2000.
4. You have agreed to evaluate the safety and immunogenicity of concomitantly administered vaccines, e.g., DTaP, *Haemophilus influenzae* type b conjugate vaccine, MMR and varicella vaccines, with a fourth dose of Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) in 12-15-month old children who previously received three doses of DTaP, IPV, *Haemophilus influenzae* type b conjugate vaccine and Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein). This study will be initiated in January 2001 as subjects in the Phase 4 safety study reach 12-15 months of age.
5. You have agreed to continue surveillance for invasive pneumococcal disease in children who received Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) in the efficacy study conducted at Northern California Kaiser Permanente.
6. You have agreed to provide comparative immunogenicity data for pertussis, *Haemophilus influenzae* type b (Hib) and poliovirus responses for children who received DTaP, Hib, IPV and Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) during the primary immunization series. We acknowledge your commitment to provide these data from a study performed in —. These data will be submitted to CBER in April 2000.
7. You have agreed to provide safety and immunogenicity data for Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) administered to high-risk children, e.g., HIV-infected infants, subjects with sickle cell disease and bone marrow transplant recipients.

We also acknowledge the following commitments outlined in your letters dated January 17, 2000, January 28, 2000, February 2, 2000 and February 16, 2000 regarding bulk manufacturing at your Sanford, North Carolina location:

8. You have agreed to perform a temperature mapping study with numerical-based acceptance criteria for the \_\_\_\_\_  
\_\_\_\_\_ The report should include thermocouple data from individual shelves, as well as between shelves with slope calculations for ramping temperatures. The study and data will be submitted to CBER by March 15, 2000.
9. You have agreed to perform repeat sterilization validation for the \_\_\_\_\_ using Biological Indicator \_\_\_\_\_ rather than Biological Indicator \_\_\_\_\_. The validation protocol and data will be submitted to CBER by March 15, 2000.
10. You have agreed to test — batches of each serotype for residual moisture and compare data obtained against stability data to set final bulk residual moisture specifications, and submit these data to CBER by February 2002.

This information will be placed in your biologics license application file for this product.

Changes in the manufacturing process, manufacturing facility, product testing, packaging or labeling for Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein) may require the submission of a supplement to your biologics license application for review and approval prior to implementation.

It is requested that adverse experience reports for Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM<sub>197</sub> Protein), be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). According to 21 CFR 600.80(c)(2) [Periodic Adverse Experience Reports], the licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals for the first 3 years following approval. Also as noted in the section, the FDA may require that these reports be submitted at different time intervals. For *Prevnar*, FDA requests that such reports be prepared for the Agency on a monthly basis (instead of quarterly) for the first year following approval and be submitted to the Agency within 30 days of the end of each month, respectively.

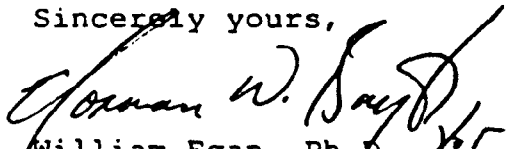
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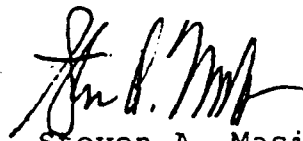
After this first year, the CFR prescribed schedule for submitting such reports should be used. Since your product is characterized as a vaccine, these reports should be submitted to the Vaccines Adverse Event Reporting System (VAERS) using the pre-addressed form VAERS-1.

Please submit three copies of final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, please submit three copies of the introductory advertising and promotional labeling. You may wish to submit the proposed materials in draft form with part I of FDA form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Two copies of final advertising and promotional materials should be submitted at the time of use with part II of FDA form 2567 to the Advertising and Promotional Labeling Staff. Please include copies of the approved labeling (package insert) with your advertising and promotional materials. Promotional claims should not be contrary to approved labeling. No comparative claims or claims of superiority over other similar products should be made unless data to support such claims are submitted to and approved by CBER.

Please acknowledge receipt of this letter to the Director, Division of Vaccines and Related Products Applications, HFM-475, Center for Biologics Evaluation and Research.

Sincerely yours,

  
William Egan, Ph.D.  
Acting Director  
Office of Vaccines  
Research and Review  
Center for Biologics  
Evaluation and Research

  
Steven A. Masiello  
Director  
Office of Compliance and  
Biologics Quality  
Center for Biologics  
Evaluation and Research